Seizure (2004) **13S**, S2–S4

ELSEVIER

www.elsevier.com/locate/yseiz

Review of zonisamide development in Japan

Masakazu Seino*

National Shizuoka Medical Institute of Neurological Science, Urushiyama 886, Shizuoka 420-8688, Japan

KEYWORDS
Zonisamide;
Epilepsy;
Japan;
Safety;
Efficacy

Summary Zonisamide is a benzisoxazole-based compound first synthesized in the early 1970s by the research laboratories of Dainippon Pharmaceutical Company in Osaka, Japan. Identified as an anticonvulsant during exploratory research, zonisamide has since been characterized as having broad-spectrum antiepilepsy and neuroprotective effects. Early clinical studies in Japan demonstrated that zonisamide has a long elimination half-life and is well tolerated; Phase II and III clinical trials established the drug's efficacy and safety for the treatment of partial and generalized seizures. In 1989, zonisamide was approved and marketed in Japan under the trade name of Excegran®. Data from postmarketing surveillance studies and clinical observations over 10 years of use have continued to support zonisamide's efficacy and safety, identified its usefulness as monotherapy, and characterized its effectiveness for various seizure types and epilepsy syndromes.

Introduction

Zonisamide, a benzisoxazole-based compound, was first synthesized in 1974 by the research laboratories of Dainippon Pharmaceutical Company during exploratory research on drugs for psychiatric disorders. Preclinical studies in laboratory animals showed that the range of zonisamide plasma concentrations suppressed maximal electroshock seizures, and that the occurrence of neurological adverse effects was broader than the range observed for phenytoin or carbamazepine.[1] These results suggested that zonisamide might also have a broader therapeutic range in humans compared to other antiepilepsy drugs (AEDs). The mechanisms by which zonisamide halts seizure activity are not fully understood, but are thought to involve suppression of voltage-dependent sodium channels and T-type calcium channels.[2,3]

Animal experiments have also demonstrated that zonisamide has neuroprotective effects. Zonisamide can prevent incipient cerebral infarction in an ischemia/reperfusion model,[4] and can inhibit degeneration of dopaminergic neurons in a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-derived model of Parkinson's disease.[5] Such effects have not been observed with carbamazepine or valproate, and suggest that zonisamide may have a free-radical scavenging effect. The neuroprotective effects of zonisamide seem to be distinct from its antiepilepsy effects.

Phase I through III trials in Japan

Phase I trials of zonisamide began in September 1979 at the National Epilepsy Center in Shizuoka. These trials, which involved healthy male volunteers, showed that zonisamide has a long elimination half-life and is well tolerated.[6]

Phase II trials commenced in 1985, followed by Phase III trials. Among the trials was a double-

*Tel.: +81 54 245 5446; fax: +81 54 247 9761.
E-mail address: seino725@mx6.mesh.ne.jp (M. Seino).

1059-1311/$30 – see front matter © 2004 Published by Elsevier Ltd on behalf of BEA Trading Ltd.
doi:10.1016/j.seizure.2004.04.015

blind study in which zonisamide was used to treat adult patients with partial seizures; carbamazepine served as the control drug.[7] Thirty-four institutions participated in this study. The data showed that during a 16-week observation period, the zonisamide treatment group exhibited improvement rates in seizure frequency, defined as >50% reduction in seizure frequency from the baseline, that were almost equal to those seen with carbamazepine treatment. In addition, zonisamide's safety profile was superior to carbamazepine. In another study that compared zonisamide and valproate in children with convulsive or nonconvulsive generalized seizures over 8 weeks of treatment, zonisamide efficacy was equivalent to that of valproate.[8]

A total of 1008 patients were engaged in Phase II and III trials of zonisamide. Examination of data for the 1008 patients showed that 72% of patients receiving zonisamide monotherapy experienced a >50% reduction in seizure frequency from the baseline (i.e., improvement rate). Improvement rates in zonisamide-treated patients were 81% for simple and complex seizures, and 67% for secondarily generalized tonic–clonic seizures.

Among the same 1008 patients, adverse effects were observed in 573 (52%), and zonisamide was discontinued in 185 (18%). Principal adverse effects were drowsiness (24%), ataxia (13%), loss of appetite (11%), gastrointestinal symptoms (7%), decrease in spontaneity (6%), and mental slowing (5%). Renal calculi were found in two patients, both of whom had a positive family history of kidney stones. The stones were discharged spontaneously, and the stone from one of the patients was a calcium salt.[9]

Application for approval to manufacture zonisamide in Japan was made in December 1987, and marketing was approved in March 1989. In June 1989, zonisamide was marketed under the trade name of Excegran®. A brief discussion of the current status of zonisamide in the Japanese AED market is provided in the sidebar. In June 1992, zonisamide was introduced in the South Korean market.

Postmarketing studies in Japan

Following the debut of zonisamide on the Japanese market, Dainippon initiated postmarketing surveillance. This surveillance was comprised of two studies—a general retrospective study and a prospective survey on long-term use. The retrospective study lasted 5 years—from April 1989 to March 1994—and data were collected for a total of 4028 patients from 459 hospitals nationwide. To assess the long-term safety and efficacy of zonisamide for treatment of epilepsy, the prospective survey studied patients for whom zonisamide had been administered for >1 year to ≤3 years. Safety data were collected for 1512 patients. Results from these studies will be detailed elsewhere in this supplement.

Personal clinical experience

In my personal experience in treating patients with various epileptic syndromes, I have found zonisamide useful as monotherapy, both for adults and pediatric patients. In addition, zonisamide is effective for simple and complex partial seizures, with or without partial-onset generalized tonic–clonic seizures. It is also effective for generalized tonic–clonic seizures, tonic seizures, atypical absence seizures, infantile spasms, and progressive myoclonus epilepsies. However, zonisamide may or may not be effective for myoclonic seizures of idiopathic generalized epilepsy.

Conclusion

Zonisamide clearly plays a key role in the treatment of epilepsy in Japan. However, Japan needs additional AEDs. Since zonisamide's introduction in 1989, no new AEDs have been approved in Japan despite extensive clinical trials of numerous AEDs, including felbamate, gabapentin, lamotrigine, tiagabine, and topiramate, all of which have received approval in other countries. The chief barrier to the introduction of new AEDs in Japan seems to be a drug administration bureaucracy that can greatly delay the approval process and the launch of new AEDs on the Japanese market. This has been a tremendous problem since the launch of zonisamide in Japan.

Zonisamide and antiepilepsy drug market in Japan

In 1998, the AED market totaled 26.7 billion yen on a drug price basis. Valproate held about 50% of the market, followed by carbamazepine and zonisamide, each with a share of slightly more than 12%. Since its introduction in 1989, zonisamide has shown a steady annual growth in market share, including a 9.5% share of the AED market in 1994, progressing to a 10.9% share in 1996 and a 12.1% share in 1998 (Table 1). These facts indicate an appraisal and acceptance of zonisamide and demon-

Table 1 Zonisamide market penetration 1994—1998.

Year	Total AED sales (¥, in billions)[a]	ZNS market share (% total sales)[a]
1994	25.7	9.5
1995	26.4	10.2
1996	26.8	10.9
1997	27.3	11.7
1998	26.7	12.1

[a] Figures are approximations.

strate zonisamide's steady, albeit gradual, penetration of the Japanese AED market.

References

1. Masuda Y, Utsui Y, Shiraishi Y, Karasawa T, Yoshida K, Shimizu M. Relationships between plasma concentrations of diphenylhydantoin, phenobarbital, carbamazepine, and 3-sulfamoyl-methyl-1,2-benzisoxazole (AD-810), a new anticonvulsant agent, and their anticonvulsant or neurotoxic effects in experimental animals. *Epilepsia* 1979;**20**:623—33.
2. Schauf CL. Zonisamide enhances slow sodium inactivation in Myxicola. *Brain Res* 1987;**413**:185—8.
3. Suzuki S, Kawakami K, Nishimura S, Watanabe Y, Yagi K, Seino M, et al. Zonisamide blocks T-type calcium channel in cultured neurons of rat cerebral cortex. *Epilepsy Res* 1992;**12**:21—7.
4. Minato H, Kikuta C, Fujitani B, Masuda Y. Protective effect of zonisamide, an antiepileptic drug, against transient focal cerebral ischemia with middle cerebral artery occlusion-reperfusion in rats. *Epilepsia* 1997;**38**:975—80.
5. Masuda Y, Ishizaki I, Shimizu M. Zonisamide: pharmacology and clinical efficacy in epilepsy. *CNS Drugs Rev* 1998;**4**:341—60.
6. Ito T, Yamaguchi T, Miyazaki H, Sekine Y, Shimizu M, Ishida S, et al. Pharmacokinetic studies of AD-810, a new antiepileptic compound, Phase I trials. *Arzneimittel-Forschung* 1982;**32**:1581—6.
7. Seino M, Okuma T, Miyasaka M, Manaka S, Takahashi R, Murasaki M, et al. Efficacy evaluation of AD-810 (zonisamide). Double-blind study comparing with carbamazepine [in Japanese]. *J Clin Exp Med* 1988;**144**:275—91.
8. Oguni H, Hayashi K, Fukuyama Y, Watanabe K, Mimaki T, Ontanara, et al. Phase III study of a new antiepileptic AD-810, zonisamide in childhood epilepsy [in Japanese]. Jpn J Pediatr 1988;41:439—50.
9. Seino M, Naruto S, Ito T, Miyazaki H. Other antiepileptic drugs: zonisamide. In: Levy RH, Mattson RH, Meldrum BS, editors. *Antiepileptic drugs*, 4th ed. New York: Raven Press; 1995. p. 1011—23.